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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Haberbosch
Serial No.	:	10/655,225 – Conf. #5684
Filed	:	September 4, 2003
For	:	3-DEAZAADENOSIE PREVENTS ATHEROSCLEROSIS AND GRAFT VASCULOPATHY
Art Unit	:	1615
Examiner	:	Carlos A. Azpuru

This is to certify that this correspondence is being filed electronically addressed to: Commissioner for Patents, P. O. Box 1450, Alexandria, Va. 22313-1450 on the date shown below

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Eileen Sheffield Date:

Commissioner for Patents
P. O. Box 1450
Alexandria, Va. 22313-1450

RULE 132 DECLARATION

Sir:

1. I am the named inventor of the presently claimed subject matter for the above-identified patent application.

2. I have read and are thoroughly familiar with the specification and pending claims, and I have reviewed the Office Action of April 9, 2009 and the references cited by the Examiner.

3. It is my understanding that the Examiner has rejected claims 18-22 and 26-44 under 35 U.S.C. §103(a) based on a combination of U.S. Patent No. 4,322,411 ("Vinegar") in view of U.S. Published Patent Application No. 2003/0203976 ("Hunter") or U.S. Patent No. 5,234,456 ("Silvestrini"), both in view of Mizuno, et al., Nucleotides. III Syntheses of deazaadenosine cyclic 3',5'-phosphates and related nucleotides of biological interest, Fac. Pharm. Sci., Hokkqido Univ., Sapporo, Japan, Chemical and Pharmaceutical Bulletin (1975),

23(8), 1664-70 ("Mizuno" hereinafter) and Ikehara, Deazaadenosine Polymers, Mitsubishi Chemical Industries Co. Ltd., Japan, Japan Kokai Tokkyo Koho, 6 pp. ("Ikehara" hereinafter).

4. The invention relates generally to the use of 3-deazaadenosine or related salts, or analogs thereof which degrade to 3-deazaadenosine in a body, to prevent various vascular diseases or graft rejection. More specifically, the presently claimed subject matter relates to a stent coated with 3-deazaadenosine or an analog of 3-deazaadenosine selected from the group consisting of a salt of 3-deazaadenosine and a precursor of 3-deazaadenosine which degrades to 3-deazaadenosine in a body under physiological conditions (See, e.g., page 4, lines 30-33 to page 5, line 1 of the specification). Methods of treating method of treating in-stent restenosis, a reperfusion injury, an infectious coronary syndrome, an inflammatory coronary syndrome, dilated cardiomyopathy, viral myocarditis or a reperfusion injury by implanting a stent coated with 3-deazaadenosine or a related salt or analog into a patient in need thereof are also claimed (See, e.g., specification page 4, lines 25-32 to Page 5, lines 1-6).

5. There is no specific teaching cited by the Examiner disclosing the use of deazaadenosine to treat the claimed disease states or conditions, i.e., stent restenosis, a reperfusion injury, an infectious coronary syndrome, an inflammatory coronary syndrome, dilated cardiomyopathy, viral myocarditis, infectious coronary syndrome, or a reperfusion injury, set forth individually or in various combinations in method claims 21-22, and 32-44. In fact, none of the cited references addresses the treatment of the various disease states with a stent that is coated with 3- deazaadenosine or analog thereof as claimed. disease states were specifically addressed by the Examiner.

6. With respect to claims 18-20 and claims 26-31 the Examiner only suggests that 3-deazaadenosine is disclosed by Vinegar, but does not suggest that any other feature is specifically disclosed, e.g., a salt of 3-deazaadenosine or a precursor which degrades to 3-deazaadenosine in the body under physiological conditions such as set for the in claims 18-20 and 26-31.

7. More specifically, the active agents 3-deazaadenosine-3'-monophosphoric acid, 3-deazaadenosine-3'5'-cyclophosphate and 3-deazaadenosine-5'-diphosphoric acid are not discussed at all by the Examiner.

8. This rejection appears to be based on improper hindsight reasoning. For reasons set forth below, at the priority date of the invention, there was no reason for one skilled in the art to combine the cited references as proposed by the Examiner.

9. An advantage of a coated stent of the invention is the provision of a medical devise capable of delivering and eluting the active ingredient 3-deazaadenosine directly at the injured vascular site.

10. Vinegar discloses that 3-deazaadenosine is a potent anti-inflammatory agent and thus suitable for the treatment of inflammation. According to Vinegar, clinical conditions with which inflammation is associated include arthritis, rheumatoid arthritis and osteoarthritis, postoperative inflammation, dental inflammation, acute and chronic ocular inflammatory diseases, and conjunctivitis. In contrast, presently claimed invention relates to the treatment of in-stent restenosis, reperfusion injury, infectious or inflammatory coronary syndrome, dilated cardiomyopathy and viral myocarditis. The skilled artisan cannot ascertain from Vinegar that 3-deazaadenosine can be used for the treatment of the claimed diseases.

11. Furthermore, according to Vinegar, 3-deazaadenosine is orally, systemically and locally active. Vinegar fails to disclose that this compound is suitable for coating stents and therefore does not teach a stent coated with 3-deazaadenosine or an analogue thereof. Furthermore, this reference does not teach a method of treating or preventing stenting-associated symptoms as claimed in present claim 21. In other words, Vinegar does not contain any teaching or suggestion to the particular application of the presently claimed invention, namely as a coating on a stent. If a skilled artisan even decided to use 3-deazaadenosine as anti-inflammatory agent in view of Vinegar, there was no motivation to use a method of administration not disclosed by Vinegar.

12. In sum, and in my opinion, neither the suitability of 3-deazaadenosine for the treatment of the particular diseases of the invention nor the administration of 3-deazaadenosine as a coating on a stent is taught or suggested by Vinegar.

13. Silvestrini describes a stent for implanting within a body lumen. Furthermore, according to Silvestrini, a stent may act as a sustained release applicator generally for anti-inflammatory drugs. Silvestrini focuses on the structure of the stent described therein, which is engineered such that the stent, when positioned and subsequently inflated, supports a lumen. A

therapeutic drug can be included for release at the site of stent placement. As disclosed in column 3, lines 15-20, non-limiting examples of such drugs include, among others, anti-inflammatory drugs. Thus, inflammatory agents are just one possibility of many agents which are suitable in principle. However, Silvestrini does not appear to provide any specific examples of anti-inflammatories which can be used in combination with the disclosed stent. More specifically, Silvestrini does not disclose 3-deazaadenosine or an analogue thereof and does not teach a stent coated with said compounds and further does not teach a method for suppressing/avoiding undesired side-effects following stenting.

14. Furthermore, Silvestrini only mentions the inclusion of anti-inflammatories for "suppression of biologic response to stenting or balloon angiography: (col. 3, lines 19-20). Silvestrini does not suggest using 3-deazaadenisone as a primary treating agent, only as an adjunct to reduce side effects of stent or angiography procedures. More specifically, Silvestrini does not disclose 3-deazaadenosine or an analogue thereof and does not teach a stent coated with said compounds and further does not teach a method for suppressing/avoiding undesired side-effects following stenting. Furthermore, Silvestrini fails to provide any hint as to covalent binding of drugs to a stent.

15. Hunter discloses anti-angiogenic compositions and anti-inflammatories, and methods for the use thereof. Hunter discloses stents which may be coated with an anti-angiogenic composition and which may additionally include other agents such as anti-inflammatories (Par. [0151]). Additionally, the anti-angiogenic composition may comprise a wide variety of compounds. Paragraph [0151] lists several kinds of active agents and names some representative examples of anti-inflammatory agents such as steroids and non-steroidal anti-inflammatory drugs. 3-deazaadenosine is not disclosed. Note that Vinegar teaches that 3-deazaadenosine is different from known anti-inflammatory agents (See col. 1, line 44 to col. 2, line 6) and may in fact be used with other anti-inflammatory agents. Thus, successful use of 3-deazaadenosine in a stent could not be predicted from the disclosure of the cited references. Hunter does not give any hint or suggestion as to coating a stent specifically with 3-deazaadenosine or an analogue thereof for treating and/or preventing stenting side-effects. Furthermore, Hunter does not give any hint or suggestion of the covalent binding of drugs to a stent.

16. Newly cited references Mizuno et al. and Ikehara each disclose 3-deazaadenosine derivatives but do not give any hint or suggestion as to the subject matter of the presently claimed invention.

17. It was an object of my presently invention to inhibit and/or prevent undesired stenting-associated side-effects. I discovered that typical stent-associated side-effects do not occur when stent implants are coated with 3-deazaadenosine or an analogue thereof. Characteristic stenting-associated side-effects are include vasculopathies as restenosis, reperfusion injury, infectious coronary syndrome, inflammatory coronary syndrome and dilated cardio-myopathy.

18. The pathophysiology of stenting-associated conditions like restenosis is multifactorial and comprises inflammation, smooth muscle cell migration and proliferation and extracellular matrix formation, all mediated by distinct molecular pathways. Molecular reasons for these vasculopathies are, amongst others, the expression of endothelial cell adhesion molecules, as for example VCAM-1 and ICAM-2 after stent implantation. As a result, apart from inflammatory reactions, especially proliferation processes are activated in the affected vascular walls, leading to neoplastic tissue growth. This neoplastic tissue extends into the lumen of the blood vessel, leading to a stenosis of the vessel. Therefore, the ideal drug to prevent side-effects of stent implantation like restenosis must have various effects, namely: 1. an anti-inflammatory effect, 2. an anti-proliferative and anti-migratory effect on smooth muscle cells, and 3. must allow re-endothelialization.

19. I discovered that 3-deazaadenosine or an analogue thereof is, apart from its already known anti-inflammatory effect (inhibition of the infiltration of monocytes into vascular walls), additionally, and above all, active in the inhibition of the expression of endothelial cellular adhesion molecules. It is exactly this inhibition which successfully prevents the proliferation processes induced by stenting, i.e. activation of cell division in the endothelial layers of the blood vessel and, consequently, vascular stenosis.

20. The aforementioned physiological reactions to stenting are especially effectively inhibited when stents are coated or covalently coated, respectively, with 3-deazaadenosine or an analogue thereof.

21. I have, for what I believe is the first time, shown the inhibiting effect of 3-deazaadenosine or an analogue thereof with regard to physiological (proliferative) processes associated with stenting as well as the efficacy of said compounds on stents coated therewith. I also discovered, for the first time, that 3-deazaadenosine inhibits the proliferation of smooth muscle cells and the cell cycle via an interaction with the Ras signal cascade.

22. The cited references neither provide to one of skill on the art at the time of my inventions any hint or suggestion as to the anti-proliferative effect of 3-deazaadenosine or an analogue thereof, which is essential for the effective prevention of stenting-associated side-effects, nor to the coating of stents with these compounds. Vinegar only discloses that 3-deazaadenosine has an anti-inflammatory effect. Vinegar is based on a patent application filed on April 25, 1980. The Examiner is invited to note that stenting associated disorders such as in-stent stenosis were not known at that time, since the first stents had primarily been implanted at the end of the 1980's. A connection between 3-deazaadenosine disclosed herein and physiological reactions associated with stenting could not, therefore be obvious to one of skill in the art based on the disclosure of Vinegar. At the priority date a person skilled in the art trying to solve the problem of the present invention would have had no motivation to consider Vinegar, since there is neither described the anti-proliferative effect of 3-deazaadenosine, nor the coating of stents with this compound.

23. Furthermore, a combination of Vinegar with either of Silvestrini or Hunter or of the other secondary references does not render the subject matter of the present invention obvious. Silvestrini and Hunter disclose stents which may be coated with anti-inflammatory agents. They do not, however, provide any hint or suggestion regarding stents coated with compounds having the pharmacological profile of 3-deazaadenosine. More specifically, the cited references do not, alone either in combination, provide any hint as to stents covered with an agent inhibiting specific physiological processes induced by stenting, i.e. inflammation, cellular migration and proliferation and extracellular matrix formation in vascular walls.

24. A person skilled in the art having knowledge of the cited state of the art and the references cited below would rather have been led away from the present invention, since it had been known from the art that anti-inflammatory drugs were not suitable to inhibit the proliferation of smooth muscle cells and, thus, stenting-induced side-effects as for example restenosis. For example site specific drug delivery of dexamethasone to porcine coronary artery

wall had no effect in treating restenosis in a study published by Park and Linkoff (Park SH, Lincoff AM, Sem Interv Cardiol 1998;3:191-195). In another study published by Wang et al. (Wang L. et al., Cor Artery Dis 2005;16:237-243), stent mediated methylprednisolone delivery reduces macrophage content, but did not reduce proliferation of smooth muscle cells. It is exactly such proliferation, however, that is to be inhibited in the treatment of undesired stenting-induced side-effects.

25. The reference cited by the Examiner fail to provide any hint regarding stenting-induced proliferation in endothelial tissue causing undesired side-effects which are to be avoided, nor to the fact that stents coated with 3-deazaadenosine are effective in the treatment of these stenting induced side-effects. Starting from Vinegar, Silvestrini and Hunter, there was, consequently, no reason for one of skill in the art coat stents with 3-deazaadenosine or a derivative thereof. Thus, in my opinion, the subject matter of the present invention is not, therefore, rendered obvious by Vinegar in view of Silvestrini and/or Hunter.

26. In summary, it is my opinion that a person skilled in the art with the goal of effectively inhibiting stent-associated side-effects would not have been motivated to combine Vinegar, Silvestrini, Hunter and/or the other cited references, since, on the one hand, he did not have the knowledge that inflammatory reactions proliferative processes should be inhibited to prevent of detrimental stent-associated side-effects. On the other hand, the cited state of the art does not disclose or suggest that proliferative processes in the vascular walls can successfully be inhibited by 3-deazaadenosine.

27. Finally, the cited references do disclose the subject matter of present claim 20, since they do not give any hint or suggestions as to the advantageous effect of stents covalently coated with 3-deazaadenosine.

28. Besides inflammatory responses, the proliferation of human coronary vascular smooth muscle cells (VSMC) comprises a major determinant in the development of atherosclerosis and restenosis. Current data show that in addition to its anti-inflammatory action, 3-deazaadenosine dose-dependently prevents the proliferation and migration of human coronary vascular smooth muscle cells (VSMC). It is only by exerting potent anti-proliferative and anti-inflammatory properties that 3-deazaadenosine provides an improved approach to prevent

vascular proliferative diseases, and this favorable effect was not known before my present invention.

29. Additionally, the subject matter of claims directed to methods of treatment with the stent of the invention is not taught or suggested by the combination of Silvestrini, Hunter and Vinegar. The claimed methods of treatment are based on the mechanism by which 3-deazaadenosine exerts its favorable effect. The suitability for the treatment and prevention of restenosis is not only due to the anti-inflammatory action of this substance. In the past, no significant prevention of restenosis could be achieved. I showed, for the first time that the application of 3-deazaadenosine significantly reduces restenosis.

30. To summarize, there is no disclosure in any of the cited references that 3-deazaadenosine shows any favorable effects when used as a coating on a stent. To my knowledge, never before had anybody tried to determine whether this substance is at all suitable for this application form. Thus, if the skilled artisan would have decided to use an anti-inflammatory agent in combination with one of the stents of Hunter or Silvestrini, he would most likely selected a drug which is commonly used in combination with stents, and, not only that, he would not have selected the anti-inflammatory as a primary therapeutic agent since they both suggest the use of an anti-inflammatory as an adjunct to a primary therapeutic. Since Silvestrini and Hunter do not give much guidance on how to select the anti-inflammatory drug, and Vinegar describes 3-deazaadenosine as a non-traditional anti-inflammatory, the skilled person would have considered documents which describe active agents for a use as coating on a stent; however, it is respectfully submitted that he would not have considered 3-deazaadenosine in this context. Only someone aware of the teaching of the presently claimed invention would be guided to use 3-deazaadenosine. The other cited references fail to overcome the problems with the aforementioned references.

31. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

By_____
Name Werner Haberbosch

22.07.2009
Date